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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,512	WOOLF, TOD M.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-76 and 78-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-76 and 78-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment after final rejection was received and entered on 4/14/06.

Claim 77 was canceled.

Finality of the previous Office Action is withdrawn in favor of the following NON-FINAL Office Action containing new grounds of rejection not necessitated by Applicant's amendment.

Claims 55-76 and 78-94 are under consideration.

Rejections Withdrawn

The rejections of claims 55-76 and 78-94 under 35 USC 112, second paragraph are withdrawn in view of Applicant's amendments.

The rejections of claims and 59, 76-82 under 35 USC 103 citing the Flower reference are withdrawn in view of Applicant's arguments indicating that Flower does not teach that fluorescein is an exchangeable alternative of the fluors used by Flower for photodynamic therapy.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 72-76 and 78-94 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reaons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 72 and dependents are drawn to a method of delivering an oligomer into the cytosol of a cell by contacting the cell with at least one oligomer and a fluorescently labeled transport peptide, allowing cellular uptake of the oligomer and the labeled transport peptide, and illuminating the cell with a wavelength of radiant energy that activates the fluorescent label thereby effecting release of the oligomer into the cytosol of the cell.

The claims as amended contain new matter because the specification and claims as filed did not contemplate a fluorescently labeled transport peptide. At page 6 of the response, Applicant asserts that claim 72 is supported by paragraphs 0011, 0034, 0055, 0065, 0089, 0106, 0114, and 0122. These paragraph numbers were interpreted by the Examiner to correspond to those in the published application (US 20030031655). However, a review of these passages reveals no support for a fluorescently labeled transport peptide.

The specification broadly supports methods of contacting cells with fluorescently labeled ligands, and teaches that the ligands can be oligonucleotides, or alternatively,

peptides. See page 3, lines 14-23 and page 4, lines 15-18, reproduced below (corresponding to paragraphs 0011, 0012, and 0022).

This invention advances the state of the prior art by providing novel methods of enhancing the availability of ligands inside a cell. Such methods are useful both in vitro and in vivo. In one aspect, the invention pertains to a method of delivering a ligand to a cell by contacting a cell with a ligand and a fluorophore; and illuminating the cell with a light that activates the fluorophore such that the ligand is delivered to the cell.

In one embodiment, the ligand is an oligonucleotide. In another embodiment, the ligand is peptide. In another embodiment, the ligand is a fluorescent virus. In still another embodiment, the ligand is a morpholino oligonucleotide. In still another embodiment, the ligand is a sense oligonucleotide. In yet another embodiment the ligand is an antisense oligonucleotide.

In one embodiment, the ligands are fluorescent oligonucleotides. In another embodiment, the ligands are fluorescent peptides. In another embodiment, the ligands are fluorescent viruses. In one embodiment, the ligands are fluorescent morpholino oligonucleotides.

The specification as filed supports linkage of transport peptides to ligands for facilitation of cellular uptake, wherein the ligands may be peptides. See page 23, lines 17-28 (corresponding to paragraphs 0088 and 0089):

In one embodiment, ligands are modified by attaching a peptide sequence that transports the olignucleotide into a cell, referred to herein as a "transporting peptide." In one embodiment, the composition includes an olignucleotide which is complementary to a target nucleic acid molecule encoding the protein, and a covalently attached transporting peptide.

The language "transporting peptide" includes an amino acid sequence that facilitates the transport of a ligand into a cell. Exemplary peptides which facilitate the transport of the moieties to which they are linked into cells are known in the art, and include, e.g., HIV TAT transcription factor, lactoferrin, Herpes VP22 protein, and fibroblast growth factor 2 [citations omitted].

The specification also discusses the process of labeling peptides in the context of "Linking of Fluorophores to Ligands. See page 31, line 6 and the paragraph bridging pages 32 and 33 (corresponding to paragraph 0122).

These passages, and the specification as a whole, do not provide support for an interpretation of a transport peptide as a "ligand" that can be fluorescently labeled. In fact the specification distinguishes between transporting peptides and ligands, indicating that transporting peptides function to facilitate the transport of a ligand into a cell. While

"ligands" may be labeled with fluorophores, there is no support in the specification for the idea that transporting peptides may be labeled with fluorophores. As a result, the specification does not contemplate a fluorescently labeled transport peptide, or a method of contacting a cell with at least one oligomer and a fluorescently labeled transport peptide. So, one of skill in the art could not conclude that Applicant was in possession of the claimed method at the time the application was filed.

It is also noted that the specification and claims as filed do not fully support the term "poly-arginine peptide" as recited in instant claim 78. This is a broad term that embraces peptides with multiple arginine residues, a few of which are disclosed in the specification, as well as arginine homopolymer peptides that are not supported by the specification. For example, the term clearly embraces e.g. a 20mer peptide composed entirely of arginine residues. There is no support for this embodiment in the specification, so claim 78 contains new matter.

Response to Arguments

Applicant's arguments filed 4/14/06 have been fully considered but they are not persuasive.

Applicant addresses the new matter rejection at pages 8-10 of the response. Applicant admits that the claim limitation "fluorescently labeled transport peptide" lacks *ipsis verbis* support in the specification, but correctly indicates that this is not required as long as the description clearly allows persons of ordinary skill in the art to recognize that the Applicant was in possession of what is claimed at the time the application was

filed. However, the specification as filed does not allow this with respect to the limitation "fluorescently labeled transport peptide". One of skill in the art would see that the specification distinguishes between transport peptides and ligands at paragraphs 88 and 89, stating that the "ligands are modified by attaching a peptide sequence that transports the [ligand] into a cell, referred to herein as a "transporting peptide", and "[t]he language "transporting peptide" includes an amino acid sequence that facilitates the transport of a ligand into a cell." So when one of skill in the art reads paragraph 122, which discusses linking fluorophores to peptides in the context of a section devoted to linking fluorophores to ligands, one of skill in the art would clearly see that this section applies to ligands and would have no reason to apply it to the transport peptides that are clearly differentiated from ligands by the specification. There is simply no suggestion in the specification that a transport peptide should be fluorescently labeled, and nothing to indicate to one of skill in the art that Applicant was in possession of this very specific limitation at the time the invention was filed. Applicant indicates that it is unduly restrictive and improper to interpret paragraph 122 in the context of the section heading under which it occurs. The Examiner disagrees. Every paragraph under the section heading "Linking of Fluorophores to Ligands" addresses methods and linkers through which fluorophores can be attached to various ligands, specifically to oligonucleotide ligands and peptide ligands. What would lead one of skill in the art to apply these teachings to transport peptides? Applicant argues in the paragraph bridging pages 9 and 10 that transport peptides certainly qualify as ligands as defined in the present invention because "ligand" includes molecules that enter cells by receptor

mediated endocytosis" and one of skill would recognize that transport peptides can enter cells by this route. This is unpersuasive because the specification clearly distinguishes between transport peptides and ligands as discussed above, indicating that transport peptides are used to modify ligands. The rejection is maintained.

Applicant addresses the term "polyarginine peptide" in claim 78 at page 10 of the response, indicating that the Examiner is improperly seeking *ipsis verbis* support. Applicant in essence argues that because the Examiner was able to think of species to which the term could be applied, but that were not supported in the specification, one of skill in the art would conclude that Applicant was in possession of these species. This is unpersuasive. The Examiner is capable of thinking of any number of things for which the specification offers no support, this hardly means that Applicant was in possession of them at the time of the invention. Support in the specification appears to limited to paragraph 84 which describes compositions for delivering ligands of the invention comprising:

-a number of arginine, lysine, histidine and/or ornithine residues linked to a lipophilic moiety, and

-a peptide having from between about one to about four basic residues located e.g., on the amino terminal, c-terminal, or internal region of the peptide, specifically exemplifying the peptide (N-term) His-Ile-Trp-Leu-Ile-Tyr-Leu-Trp-Ile-Val-(C-term). However, the claim term "polyarginine peptide", which has no *ipsis verbis* support, would clearly indicate to one of skill in the art that peptides outside the genus of peptides having "from between about one to about four basic residues located e.g., on

the amino terminal, c-terminal, or internal region of the peptide" are embraced by the claim. Such peptides include any peptide having more than 4 arginines such as homopolymers of arginine. The specification as filed simply does not suggest homopolymers of arginine, or any peptide comprising more than about 4 arginines, to one of skill in the art. Therefore one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 72, 74, 75, and 83-87 are rejected under 35 U.S.C. 102(e) as being anticipated by Berg et al (US Patent 6,680,301, issued 1/20/04).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule from endosomes and into the cytosol. See abstract. Molecules for delivery include DNA or RNA, including ribozymes. See column 2, lines 18-24, and claim 3 at

column 23. Ribozymes are double stranded to the extent that they form intrastrand double helices. Delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38. These are considered to be "transport peptides" as recited in e.g. claim 72 because they facilitate transfer of negatively charged nucleic acids into cells by neutralizing their negative charge. Note also that instant claim 78 defines polyarginines as transport peptides. In one embodiment the photosensitizer is conjugated to the carrier, so Berg is considered to teach a fluorescently labeled transport peptide. See column 2, lines 50-54. Fluorophores include phthalocyanines and napthalocyanines. See e.g. claim 4 at column 23. The wavelength of light used will naturally vary with the photosensitizer used. Berg exemplified excitation with visible 450-490 nm light for 10 seconds. See column 13, lines 13-21.

Thus Berg anticipates the claims.

Response to Arguments

Applicant's arguments filed 4/14/06 have been fully considered but they are not persuasive.

Applicant addresses the 102 rejection over Berg at pages 10-12 of the response. Applicant argues that the Berg does not teach a fluorescently labeled transport peptide as the present claims require. Applicant states that a careful reading of column 2, lines 51-54 of Berg shows that the photosensitizers of Berg may be conjugated to "suitable carriers" rather than fluorescent labels as the present claims require. This is confusing,

because Applicant's argument seems to depend on the notion that the photosensitizers of Berg are not fluorescent themselves. In fact, as indicated in the rejection, the photosensitizers of Berg are fluorescent. Evidence of this fact was provided at pages 4 and 5 the Action mailed 3/23/05, i.e. in the Weizman et al (2000) and Moan et al (1998) references. There is no need for the photosensitizers to be conjugated to any fluorescent label, because the photosensitizers are the fluorescent label. Applicant then appears to argue that the photosensitizers of Berg differ from the fluorescent labels of the present invention because they are excited into a triplet state, whereas the fluorescent labels of the instant invention are excited into a singlet state. This is unpersuasive because Applicant is arguing limitations that are not in the claims. The rejected claims place no limitation on the possible excitation state of the recited fluorophore. Applicant's arguments at the last paragraph of page 11 and the first paragraph of page 12 concern the activity of FITC as a fluorophore in the experiments of Berg. These arguments are irrelevant to the rejection the rejection does not rely on the use of FITC as a fluorophore. The experiments referred to by Applicant use the fluorophores $AlPcS_{2a}$ or $TPPS_{2a}$. Applicant seems to require that the "fluorophore" of Berg must be FITC and not $AlPcS_{2a}$ or $TPPS_{2a}$. There is no basis for this requirement in the rejected claims, which do not limit the identity of the fluorophore.

In the last paragraph of page 12 applicant argues that Berg does not enable one of skill in the art to make and use the presently claimed invention. Applicant's arguments relying on limitations that are not claimed, i.e. the use of FITC rather than $AlPcS_{2a}$ or $TPPS_{2a}$ as a fluorophore, are unpersuasive for the reasons set forth above.

Applicant also states that Berg is silent towards transport peptides other than polyarginine. It is unclear to the Examiner how this would affect the enablement of Berg. Does Applicant mean to suggest that polyarginine will not function as a transport peptide? There is no evidence to support this notion, and in any case, Applicant's statement is incorrect because Berg discloses the use of polylysine as a transport peptide in working examples and throughout the specification, see Figs. 15, 17-24, 27, and 28.

Applicant asserts that Berg is silent toward conjugating the fluorescent molecule to any type of transport peptide. This is unpersuasive. Delivery-facilitating carrier molecules comprising basic amino acids, such as polylysine and polyarginine, are present in the complexes of Berg. See column 7, lines 31-38. These are considered to be "transport peptides" as recited in e.g. claim 72 because they facilitate transfer of negatively charged nucleic acids into cells by neutralizing their negative charge. In one embodiment the photosensitizer is conjugated to the carrier, so Berg is considered to teach a fluorescently labeled transport peptide. See column 2, lines 50-54.

Applicant also states that Berg is silent towards correlating any fluorescent labels with an excitation wavelength that will facilitate release of the oligomer into the cytosol of a cell without causing cytotoxicity. Applicant is arguing limitations that are not in the claims. No rejected claim excludes a cytotoxic effect, and in any case, Applicant has presented no evidence that one of skill in the art could not easily adjust the amount of photosensitizer, or light exposure, in Berg to avoid toxicity. In fact the claims of Berg, which are presumed to be enabled, require that the cell is not killed.

Finally, Applicant argues that a photosensitizing agent of Berg would be required to release oligomers into the cytosol of the cell and that fluorescent labels alone will not suffice. It is unclear how this statement affects the enablement of Berg. As discussed above, the photosensitizers of Berg ($AlPcS_{2a}$ and $TPPS_{2a}$) are fluorophores. There is no need for FITC or any other fluorescent label, because the photosensitizers of Berg meet the instant "fluorophore" limitation. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55, 57-64, 72, 74, 75, and 83-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) in view of Fire et al (US Patent 6,506,559, issued 1/14/03).

Berg taught a method for releasing molecules into the cytosol of cells by allowing the molecules to be taken up into endosomes, treating the cells with a fluorescent photosensitizer that can be conjugated to the molecule to be released, and which localizes to endosomes, and exposing the cells to light of a wavelength that excites the fluorescent photosensitizer, resulting in release of the molecule from endosomes and into the cytosol. See abstract. Molecules for delivery include DNA or RNA, including antisense oligonucleotides for disrupting gene expression. See column 2, lines 18-24,

and claim 3 at column 23. Fluorophores include phthalocyanines and napthalocyanines. See e.g. claim 4 at column 23. Delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38. These are considered to be "transport peptides" as recited in e.g. claim 72. In one embodiment the photosensitizer is conjugated to the molecule to be delivered, or to a carrier, ensuring simultaneous contact with the cell of the photosensitizer and molecule to be delivered. See column 2, lines 50-54. The wavelength of light used varies with the excitation characteristics of the photosensitizer used. Berg exemplifies excitation with visible 450-490 nm light for 10 seconds. See column 13, lines 13-21.

Berg did not teach double stranded oligonucleotides of 20-30 nucleotides in length.

Fire taught methods of inhibiting protein expression by administration of double stranded RNAs of at least 25 nucleotides.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the double stranded oligonucleotides of Fire for the antisense oligonucleotides of Berg because Fire taught that double stranded RNA oligonucleotides had numerous advantages over antisense oligonucleotides for purposes of inhibiting protein expression. For example, Fire taught that the double stranded oligonucleotides were more stable than antisense, and about 100-fold more effective than antisense at inhibiting protein expression (see column 3, lines 19-34 and column 5, lines 15-30). It would have been obvious to fluorescently label the

polyarginine carrier protein of Berg, because Berg suggested that carrier molecules can be modified that way. See e.g. column 2, lines 61-64. Note that the instant specification at paragraph 89 defines "transporting peptide" as an amino acid sequence that facilitates the transport of a ligand into a cell. This is considered to embrace the polyarginine of Berg which facilitates transfer of negatively charged nucleic acids into cells by neutralizing their negative charge.

Claim 59 is included in this rejection because the oligonucleotides of Berg were labeled with FITC, delivered to cells, and then irradiated with excitatory light. It would have been obvious to similarly label the dsRNA oligos of Fire in order to visualize their location with in the cell. The claimed invention would have been obvious regardless of whether or not transfer of the dsRNA oligonucleotides from the endosomes to the cytosol was subsequently detected because all of the active method steps were obvious, i.e. contacting the cell with a dsRNA oligomer and a fluorescein fluorophore, allowing uptake by the cell, and irradiating the cell with radiant energy at a wavelength that activates the fluorophore. See Example 13 of Berg at column 12, lines 15-54.

Claims 56 and 73 stand rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57-64, 72, 74, 75, and 83-87 above and further in view of Summerton (Biochim. et Biophys. Acta 1489: 141-158, 1999).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the

cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

While Fire also taught that the oligonucleotides may contain modified bases, the combined references did not teach morpholino modifications.

Summerton taught that morpholino modifications increase oligonucleotide resistance to nucleases. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention use morpholino oligonucleosides in the RNAs of Fire. One would have been motivated to do so in order to increase the resistance of the oligonucleotides to extracellular nucleases that might prevent delivery of intact oligonucleotides to cells.

Claims 65 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57-64, 72, 74, 75, and 83-87 above and further in view of Parker al (US Patent 4,541,438, issued 9/17/85).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg as modified by Fire because Berg taught that any light source capable of emitting the appropriate wavelength light could be used. See column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 66-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57-64, 72, 74, 75, and 83-87 above and further in view of Pandey (US Patent 5,002,962).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

Although Berg taught that fluorophores could be conjugated to oligonucleotides and carriers, Berg was silent as to the nature of the conjugation. It is fair to interpret conjugation broadly as encompassing both covalent and non-covalent means since these are both widely known in the art. Thus, Berg taught a genus embracing the instantly claimed species, but did not explicitly teach the claimed species.

MPEP 2144.08 indicates that an obviousness rejection may be appropriate in such instances, and directs the Examiner to, as always, a) consider the scope and contents of the prior art, b) ascertain the differences between in the prior art and the clams at issue, c) determine the level of skill in the pertinent art, and d) evaluate evidence of secondary considerations. Steps a) and b) are carried out above. The level of skill in the pertinent art is evidenced by Pandey. The teachings of Pandey make it evident that it was routine in the art at the time of filing to conjugate photosensitizers to other molecules by covalent means. See column 9, lines 20-31.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention, absent secondary considerations to the contrary, to covalently conjugate the photosensitizers of Berg to either oligonucleotides or carriers. One would have been motivated to conjugate to the oligonucleotides to ensure that the

oligonucleotide and photosensitizer arrived in the same cell, covalent bonds being generally more stable than non-covalent conjugation means.

Thus the invention as a whole was prima facie obvious.

Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57-64, 72, 74, 75, and 83-87 above and further in view of Pandey (US Patent 5,002,962) and Parker al (US Patent 4,541,438, issued 9/17/85).

The teachings of Berg, Fire, and Pandey are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a covalently conjugated fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg as modified by Fire because Berg taught that any light source capable of emitting the appropriate wavelength light could be used, and because Berg taught the use of

tetraphenylporphine sulfonate fluorophores. See column 6, lines 44-49, and column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 89-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57-64, 72, 74, 75, and 83-87 above and further in view of Priest (US Patent 5,391,723).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore conjugated to a carrier molecule such as polylysine or polyarginine, allowing uptake of the RNA and the fluorophore into the cell, and

irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach an oligomer covalently linked to a fluorescently labeled transport peptide.

Priest taught the use of pH-sensitive covalent linkers to attach double stranded oligonucleotides to targeting proteins for delivery to cells. See abstract, and claim 1 at column 18.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the linkers of Priest to covalently conjugate the oligonucleotides of Fire to the polylysine or polyarginine carrier of Berg. Covalent linkage would ensure complex formation between the oligonucleotide and the carrier, and the linkers are designed to degrade in lower pH environments such as endosomes, thereby releasing the nucleic acids from the carriers. See Priest at column 7, lines 24-36. One would have been motivated to attach a fluorescent photoactivator to the targeting protein, because Berg suggests that carrier molecules can be modified that way. See e.g. column 2, lines 61-64.

Thus the invention as a whole was prima facie obvious.

Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57-64, 72, 74, 75, and 83-87 above and further in view of Priest (US Patent 5,391,723) and Parker al (US Patent 4,541,438, issued 9/17/85).

The teachings of Berg, Fire, and Priest are summarized directly above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a covalently conjugated, fluorescently labeled transport protein, allowing uptake of the RNA and the fluorescent transport protein into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm.

These references did not teach a flexible endoscopic light source.

Parker taught an endoscopic light source capable of delivering excitatory wavelengths of light for tetraphenylporphine sulfonates. See Figs. 4 and 5; and column 5, lines 33-44; and claims 22 and 30.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the endoscopic light source of Parker in the invention of Berg as modified by Fire because Berg taught that any light source capable of emitting the appropriate wavelength light could be used, and because Berg taught the use of tetraphenylporphine sulfonate fluorophores. See column 6, lines 44-49, and column 7, lines 9 and 10. As such, Berg considered all such light sources to be equivalent. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on

its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was prima facie obvious.

Claims 59 and 76-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Kenney et al (US Patent 5,166,197, issued 11/24/92).

The teachings of Berg and Fire are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm. Pertinent to claims 77 and 78, Berg taught that delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38.

These references did not teach the use of fluorescein.

Kenney taught that dyes such as fluorescein, phthalocyanines, and porphyrins are all photosensitizers. Kenney taught that these dyes functioned when contacted by excitatory light that to cause the formation of singlet oxygen. See column 1, lines 56-67.

This principle is also disclosed by Berg at column 1, lines 34-53, and column 6, lines 1-43.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use fluorescein as a photosensitizer in the invention of Berg because Kenney taught that fluorescein functions similarly to the fluorescent activators of Berg, i.e. by producing singlet oxygen that can damage membrane components in close proximity to the fluor. As such, fluorescein is a functional equivalent of the flours of Berg. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Because Berg teaches that the photosensitizer may be conjugated to the oligonucleotide delivery complex, it follows that the photosensitizer will localize to the endosomes with the oligonucleotide complex. So, one would have a reasonable expectation that the fluorescein would function to degrade the endosomes when contacted with excitatory light.

Thus the invention as a whole was prima facie obvious.

Claims 79, 80, and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74,

75, 77, 78, and 83-87 above and further in view of Kenney et al (US Patent 5,166,197, issued 11/24/92) and Baetge et al (US Patent 6,451,601).

The teachings of Berg, Fire, and Kenney are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA and a conjugated fluorescein fluorophore, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm. Berg also taught that delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38.

These references did not teach SEQ ID NO: 2, antennapedia protein, or VP22.

Baetge taught that polylysine, antennapedia, TAT, and VP22 functioned similarly in that they facilitated translocation of attached molecules across membranes.

It would have been obvious to one of ordinary skill in the art at he time of the invention to substitute the antennapedia or VP22 proteins of Baetge for the polylysine of Berg because Baetge taught that these peptides functioned as membrane translocation sequences. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on

its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case it would have been obvious to use either VP22 or antennapedia instead of polylysine because the prior art recognized that these peptides all performed a similar function. Although Baetge does not explicitly discloses SEQ ID NO: 2, this disclosure is considered to be inherent because the instant specification states that this sequence is a fragment of antennapedia. Absent evidence to the contrary, it is comprised by the antennapedia protein of Baetge.

Claims 79-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Berg et al (US Patent 6,680,301, issued 1/20/04) and Fire et al (US Patent 6,506,559, issued 1/14/03) as applied to claims 55, 57, 58, 60-64, 72, 74, 75, 77, 78, and 83-87 above and further in view of Kenney et al (US Patent 5,166,197, issued 11/24/92), Baetge et al (US Patent 6,451,601), and Rosenecker et al (US Published Application 20030125242, published 7/3/2003).

The teachings of Berg, Fire, Kenney, and Baetge are summarized above and render obvious methods of delivering to the cytosol of a cell a double stranded RNA by contacting the cell with the RNA, a conjugated fluorescein fluorophore, and a delivery peptide such as polylysine, polyarginine, antennapedia, TAT, or VP22, allowing uptake of the RNA and the fluorophore into the cell, and irradiating the cell with excitatory light that activates the fluorophore, leading to release of the RNA into the cell cytoplasm. Berg also taught that delivery-facilitating molecules comprising basic amino acids, such

as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38.

These references did not teach transportan protein or SEQ ID NO: 3.

Rosenecker taught that HIV-TAT, Antennapedia, and Transportan were functionally equivalent for the purpose of transferring molecules into cells. See Summary of Invention paragraph 11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the transportan peptide of Rosenecker for the antennapedia, VP22, or TAT of Baetge, because Rosenecker taught that HIV-TAT, Antennapedia, and Transportan were functionally equivalent. Although Rosenecker does not explicitly discloses SEQ ID NO: 3, this disclosure is considered to be inherent because the instant specification states that this sequence is a fragment of antennapedia. Absent evidence to the contrary, it is comprised by the antennapedia protein of Rosenecker.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant addresses the obviousness rejection over Berg and Fire at page 13 of the response. Applicant reiterates the arguments against Berg raised against the 102 rejection. These are unpersuasive for the reasons set forth above. Applicant also alleges that there is no motivation to combine the cited references. This is unpersuasive because Applicant did not address motivation provided in the rejection, i.e. Berg taught the use of the method to deliver antisense oligonucleotides, but Fire

taught that double stranded RNA oligonucleotides had numerous advantages over antisense oligonucleotides for purposes of inhibiting protein expression. It follows that one of ordinary skill would have been motivated to substitute double stranded RNA oligonucleotides for antisense oligonucleotides in order to obtain the advantages taught by Fire.

Applicant responds to the rejection of claims 56 and 73 over Berg, Fire, and Summerton at page 14, reiterating the arguments against Berg and Fire that are unpersuasive for the reasons set forth above. Applicant also argues that there is no evidentiary basis for the Examiner's motivation statement that one would use morpholino oligonucleotides to increase resistance to extracellular nucleases. This is unpersuasive because the Examiner is allowed to use sound scientific reasoning to establish a case of prima facie obviousness. Applicant has failed to point out why this reasoning is unsound. Applicant also argues that the references cannot be combined with a reasonable expectation of success, because the photosensitizers of Berg would be required. This argument is unpersuasive. It is true that the photosensitizers would be required, in fact the rejection depends on their inclusion since they meet the fluorophore limitation. Applicant has provided no logical reason why one would not have had a reasonable expectation of success.

The rejection of claims 65 and 68 over Berg, Fire, and Parker is addressed at page 16. Applicant reiterates the arguments applied to Berg and Fire, which are unpersuasive for the reasons set forth above.

The rejection of claims 66-70 over Berg, Fire and Pandey is addressed at pages 16 and 17. Applicant argues that the photosensitizers of Berg and Pandey are not the fluorescent labels of the instant invention. This is unpersuasive because, as discussed at length above, the photosensitizers of Berg are fluorescent. The instant claims do not exclude the fluorophores of Berg. As a result the rejected claims read on the method of Berg as modified by Fire and Pandey. Applicant also asserts there is no motivation to combine the references with a reasonable expectation of success, but fails to support this assertion with any reason. The motivation to combine is clearly addressed in the rejection above.

The rejection of claim 71 over Berg, Fire, Pandey and Parker is addressed at pages 17 and 18. Applicant reiterates arguments applied to Berg and Fire, which are unpersuasive for the reasons set forth above. Applicant also asserts there is no motivation to combine the references with a reasonable expectation of success, but fails to support this assertion with any reason. The motivation to combine is clearly addressed in the rejection above.

The rejection of claims 89-93 over Berg and Fire in view of Priest is addressed at pages 20 and 21. Applicant reiterates arguments applied to Berg and Fire, which are unpersuasive for the reasons set forth above. Applicant also asserts there is no motivation to combine the references with a reasonable expectation of success, but fails to support this assertion with any reason. The motivation to combine is clearly addressed in the rejection above.

The rejection of claim 94 over Berg and Fire in view of Priest and Parker is addressed at pages 20 and 21. Applicant reiterates arguments applied to Berg and Fire, which are unpersuasive for the reasons set forth above. Applicant also asserts there is no motivation to combine the references with a reasonable expectation of success, but fails to support this assertion with any reason. The motivation to combine is clearly addressed in the rejection above.

The arguments against the Flower reference, previously used in rejections of claims 59, 76, and 78-82 were considered persuasive. These rejections have been withdrawn and replaced by rejections citing the Kenney reference in place of the Flower reference. Applicant's arguments against the rejections citing the Flower reference have been considered as they might apply to these new grounds of rejection, but they are not persuasive. Applicant argues at page 15 of the response that one of skill would not conclude that fluorescein is a functional equivalent of the fluors of Berg. However, the cited art shows that the fluors of Berg are photosensitizers, i.e. they function by causing the production of singlet oxygen when excited, and that this causes membrane damage. It is evident from Kenney that fluorescein, like phthalocyanines, and porphyrins, is also a photosensitizer, and that it has been used as such. So it is clear that it is an art recognized functional equivalent of these molecules.

Pertinent to the rejection of claims 79, 80, and 82 over Berg, Fire, Kenney, and Baetge, Applicant argues at pages 18 and 19 that Baetge is not properly combinable. Applicant argues that Baetge taught fusion proteins comprising translocation moieties, whereas the instant claims do not require fusion proteins. This is unpersuasive

because the instant claims do not exclude fusion proteins either. Applicant argues that because Baetge discloses the transport of proteins across membranes, one wishing to transport oligonucleotides would not have been motivated to review Baetge, much less combine the teachings with the other references. This is unpersuasive because Baetge also taught the use of these peptides to transfer nucleic acids across membranes. See column 3, lines 29-34. Also, Berg taught that one could use delivery-facilitating molecules comprising basic amino acids, such as polylysine and polyarginine, may also be present in the complex. See column 7, lines 31-38. One of ordinary skill in the art appreciates that there are many well known species of the genus of delivery-facilitating molecules comprising basic amino acids. This is evidenced by Baetge who taught that polylysine, antennapedia, TAT, and VP22 functioned similarly. Applicant's arguments of hindsight reconstruction are unpersuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). This applies as well to Applicant's arguments as they might apply to the rejection of claims 79-82 over Berg, Fire, Kenney, Baetge, and Rosenecker.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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